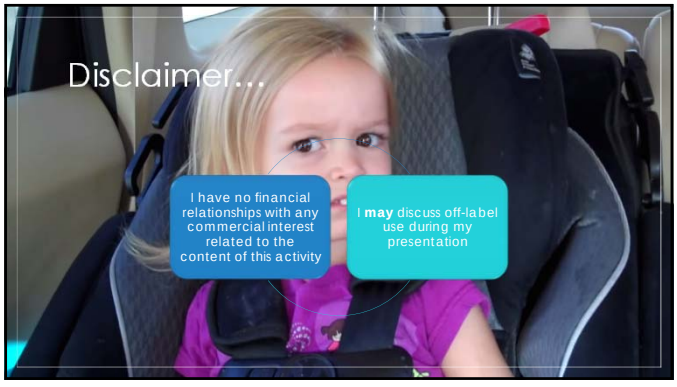
REVIEW OF OPIOID PHARMACOLOGY

With a Report on the State of the Opioid Crisis in the U.S.

Session Objectives

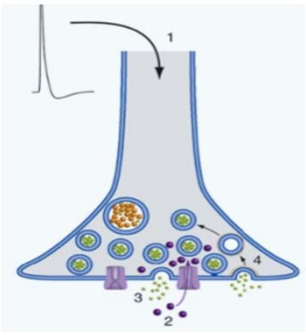
- In this session, there will be a review of general opioid pharmacology; there will also be an overview of the current state of the opioid crisis in the US
  - Review of general opioid pharmacology
  - Briefly describe the mechanisms underlying opioid hyperalgesia
  - Briefly describe opioid tolerance /dependence
  - Review of opioid addiction potential and relevant statistics



- How do we understand the neurobiology of the opioid system??
- We must start at the beginning… with pain cellular/receptor targets.

Neuronal Transmission Review

- Any level of depolarization → some Na^+ channels opening
- Adequate depolarization → inward Na^+ current > outward K^+ current
- Threshold reached for other Na^+ channels to open → rapid increase in Na^+ G → most available Na^+ channels now open (Na^+ G > 50X that of K^+ G)
- K^+ channels are also triggered to open by depolarization, but more slowly
- Membrane potential →almost reaches V_{Na}
- Na^+ channels are unstable in open state and inactivate
- K^+ channels (delayed rectifier) now open: hyperpolarizes RMP to near V_K
- Repolarization allows for Na^+ channels to return to ready, resting state

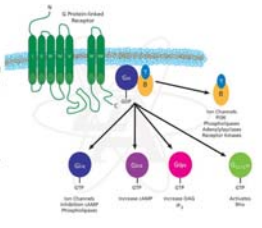


Synaptic Review

- 1 - Depolarization of the presynaptic active zone
  - Opening of VG Ca^{2+} channels
- 2 - Ca^{2+} influx →
- 3 - Vesicle exocytosis of small nearby vesicles and neurotransmitter release
  - Sustained, repetitive action potentials are required for large vesicle exocytosis (more Ca^{2+})
- 4 - Vesicle membrane endocytosis (recycling)

G-Protein-Coupled Receptor (GPCR)

- The largest family of integral membrane protein involved in many biological process and pathologies;
- 50% of all modern drugs and 25% of the top 200 best selling drugs are estimated to target GPCRs;
- Transduce the signals mediated by diverse signaling molecules, such as ions, peptides, lipids and photons, to induce different intracellular function;
- Bind their ligand and to activate different G proteins;



Opioid Receptors

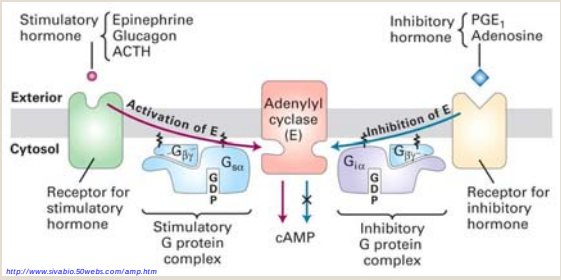
WIDELY DISTRIBUTED

- Brain, spinal cord
  - ACC
  - PAG
  - LC
  - RVM
- Peripheral neurons
- Digestive Tract

Cellular Signaling

- First messengers →
  - Extracellular signaling molecules
  - Neurotransmitters, hormones, neuropeptides, drug ligands
    - Norepinephrine, serotonin, substance P, CGRP, glutamate, GABA, histamine, opioids
- These bind the extracellular side of receptors which are coupled to G proteins
- G proteins activate → conformational change
- The active state stimulates a portion of that G protein to relay the intracellular signal to an effector complex
  - E. g. → Adenylate cyclase, phospholipase C, phospholipase A, etc.
- Intracellular production of second messengers
  - cAMP, cGMP, IP_3, Ca^{2+}
  - Arachidonic acid
  - Diacylglycerol (DAG), phosphate inositol family
- Second messengers then trigger some physiologic change downstream
- Often coupled to kinase cascades → magnification of initial first messenger signal (PKA, PKC, PKG)

General Example of 2nd Messenger System



http://www.sivabio.50webs.com/amp.htm

Opioid Pharmacology Review

- Major opioid receptors
  - μ (μ_1 μ_2 μ_3)
  - κ, δ and σ (most texts no longer list σ as an opioid receptor)
  - NOR, ZOR subtypes
- Opioid receptors coupled to G_i proteins
- Agonist binding → overall effect of membrane hyperpolarization
  - Adenylate cylcase inhibition → reductions in intracellular cAMP
  - Activation of phospholipase C (PLC)
- Inhibition of voltage-gated calcium channels
- Activation of rectifying K^+ channels (stabilizes RMP)

Activated Opioid Receptor Effects

A hyperpolarized membrane is further from depolarization (and action)

- Inhibition of AC decreases cAMP → less excitatory transmission
- Enhanced outward K^+ → hyperpolarized (postsynaptic) membrane
- Diminished Ca^{2+} current in presynaptic terminal → diminished neurotransmitter release via exocytosis
- Inhibition of PLC → decreased vesicle exocytosis
- Inhibition of PLC → decreased arachidonic acid cascade products
- Questionable effects on chloride conductance and flow → ICF
  - Hyperpolarization of neuronal membrane

Main Opioid Sites of Action…*NOT the only*

- Systemic and neuraxial opioids act via spinal dorsal horn neurons (substantia gelatinosa in Rexed's lamina II)
- Descending inhibitory pain modulation (midbrain periaqueductal gray – PAG)
  - Pontine, medullary and midbrain areas
  - Limbic system connections
  - Cortical areas, including the reward system
- Act on somatic and sympathetic peripheral nerves
- Act on GI tract tissue via receptors there
- Present on some primary sensory nerves (unknown function)

Opioid Receptors

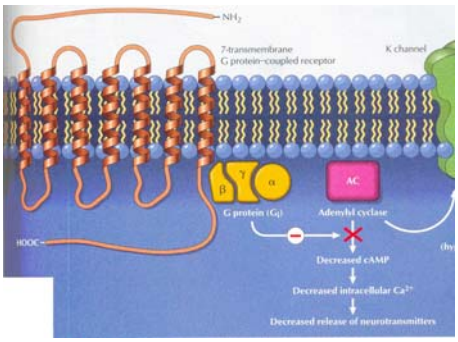
Receptor	Location	Effect	Agonists
μ_1	Brain – cortex, thalamus, PAG, ventromedial medulla Spinal cord (SG) Peripheral sensory Intestinal tract	Supraspinal analgesia Spinal analgesia Physical dependence *Nausea* Muscle rigidity Euphoria	Morphine, fentanyl *β-endorphin, met-enkephalin*
μ_2 and μ_3	Brain – as in μ_1 as well as pontine areas, raphe nuclei Spinal cord Peripheral sensory neurons Intestinal tract	Supraspinal analgesia *Respiratory depression* *Physical dependence* Muscle rigidity, miosis, urinary retention, GI motility effx, ? vasodilation	Morphine, fentanyl *β-endorphin, met-enkephalin*

Opioid Receptors

Receptor	Location	Effect	Agonists
δ (delta, DOR)	Brain – pons, amygdala, deep cortex Peripheral sensory neurons ? Spinal cord	Supraspinal and spinal analgesia Convulsant effx Dysphoria Hallucinations Pulmo stimulation CV depression	Pentazocine Nalorphine Ketamine
κ (KOR) *(can → feedback inhibition of endogenous opioids)*	Brain – hypothalamus, PAG Spinal cord Peripheral sensory neurons	Sedation, *dysphoria*, depression Spinal analgesia Less dependence, anticonvulsant effx	Morphine, nalbuphine, butorphanol, oxycodone *dynorphin*

Opioid Receptors

Receptor	Location	Effect	Agonists
Nociceptin receptor NOR	Brain – cortex, amygdala, hippocampus, septal nuclei, habenula, hypothalamus Spinal cord Peripheral neurons	Anxiety, nociception Fear-learning Depression Appetite Development of tolerance to μ agonists	Buprenorphine Etorphine (vet only) *Nociceptin*
ζ Opioid receptor ZOR OGFr	Heart, liver, skeletal muscle, kidney, brain, pancreas Fetal tissue	Tissue growth effx: Embryonic growth, wound repair, cancer cell proliferation, angiogenesis	*Met^5-enkephalin*



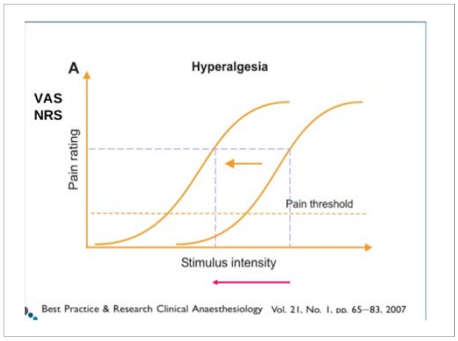
Summary: Opioid Action

- Activation of opioid receptors inhibits presynaptic release and postsynaptic response to neurotransmitters
  - Exogenous opioids
  - Endogenous opioids

Other Considerations w/ Opioids

Opioid Hyperalgesia Cellular Mechanisms

- Chronic opioid use eventually increases the activity of AC
  - Increased cAMP → decreased K^+ outflow, increased Ca^{2+} entry, increasing excitatory transmission
- Chronic opioid use activates various protein kinases, including PK-C
  - Upregulation of NMDA receptors with upregulation of VGSCs
  - Downregulation of opioid receptors
- Exogenous opioids directly activate NMDA receptors
- Some exogenous opioid metabolites directly stimulate hyperalgesia and allodynia
- Microglial activation by opioids → neuro-inflammation and pain sensitivity
- Genetic alterations induced by these changes → excitatory transcription factors → increased expression of calcitonin gene-related peptide (CGRP) & substance P
- Increased conductance at NMDA and AMPA receptors, and decreased conduction at GABA receptors



Opioid Induced Hyperalgesia

- Heightened and paradoxical perception of pain in patients receiving opioids
  - Chronic opioid Rx
  - Acutely exposed to highly potent opioids
- This sensitization is directly due to
  - Opioid use
  - In the absence of disease progression **or** withdrawal of opioid therapy

Clues to Opioid Induced Hyperalgesia

OIH may differ from previous pain in quality, location, distribution, intensity

- Pathological or neuropathic pain is typically distributed dermatomally or anatomically
  - OIH may be more generalized in nature
- OIH may worsen with opioid dose increases
- Consider OIH when there is an inexplicable pain increase after a period of effective opioid analgesia
- Consider OIH when previous opioid dose increases fail to improve chronic pain, or even worsens it

Other Issues: Opioids in Patients with Cancer

- Opioids have long been believed to be a general immune system suppressant on innate and acquired immune responses
  - Truth is more complex (Combination: immune stimulation and depression)
- Since around 2009, and declaratively since 2012, links between opioid use and rates of cancer tumor growth, progression and metastasis have been found
  - Effx on angiogenesis, vascular permeability and metastatic tendencies
- These effx are focused on the μ and the ζ opioid receptors
- Appears to be linked to both exogenous and endogenous opioids

Future targets for cancer research, alterations in oncology analgesia

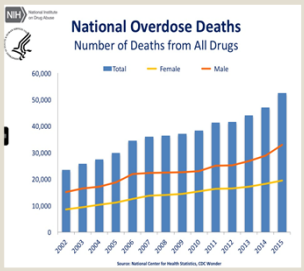
Other Issues: Opioid Tolerance/Dependence

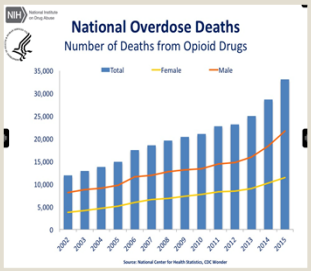
- **Opioid tolerance**: a relative loss of analgesic potency that → increasing dose requirements and ∆ a loss of efficacy over time
  - This can be innate (single nucleotide polymorphisms) or acquired
  - Tolerance develops because CNS cells with opioid receptors gradually become less responsive to the same level of circulating opioids
  - Reward system in the nucleus accumbens up-regulates (dopamine release)
- **Physical dependence**: repeated exposure to opioids, especially in escalating doses, → brain functions normally ONLY when that dose of opioids is present. Otherwise withdrawal symptoms set in
  - Withdrawal symptoms is largely an effect of resetting the tonic function of the locus ceruleus → excessive secretion of norepinephrine

Other Issues: Opioid Addiction

- Physical dependence can occur without addiction, and involves the development of tolerance and the need for certain levels of drug to avoid withdrawal S & Sx
  - Dependence develops when the neurons adapt to the repeated drug exposure and only function normally in the presence of the drug. When the drug is withdrawn, several physiologic reactions occurs
- Psychological dependence is linked with emotional and motivational withdrawal symptoms if the drug is withdrawn (mesolimbic fxn)
- Addiction is generally acknowledged to have four main components (the 4 C's): **C**ompulsive use, inability to **C**ontrol level of use, psychological **C**raving, and **C**ontinued use of drug despite its adverse effx or costs
  - Chronic
  - Loss of self-control
  - Overwhelming compulsion to use the substance

Sobering Facts





Cost of Opioid Addiction

- *> 40 Americans die each day from prescription opioid ODs*
- *In 2013, nearly 2 million Americans met criteria for opioid abuse and dependence*
- *$7.7 billion in criminal justice-related costs (state/local)*
- *¼ of the costs are borne by the public sector (Medicare/Medicaid/VHS/other government sources)*

	Health Care	Overall	Year Estimate Based On
Tobacco[1,2]	$168 billion	$300 billion	2010
Alcohol[3]	$27 billion	$249 billion	2010
Illicit Drugs[4,5]	$11 billion	$193 billion	2007
Prescription Opioids[6]	$26 billion	$78.5 billion	2013

White House Opioid Fact Sheets

- More Americans die each year from drug overdoses than motor vehicle crashes
- Majority of the overdoses involve prescription medications
- Health care providers wrote 259 million prescriptions for opioid pain medications in 2012 – enough for every American adult to have a bottle of pills

- Obama administration instituted additional actions to address the opioid epidemic
- March 2016 the White House called for opioid prescriber education to be included in healthcare provider education
- 60 Medical Schools signed a pledge to require prescriber education beginning Fall 2016 as a requirement for graduation (to include CDC Guidelines for Prescribing Opioids for Chronic Pain)

Opioid Crisis → National Emergency

- August 10, 2017: Trump declared the opioid crisis a national emergency
- Two days after the presidential opioid commission recommended this action
- 142 deaths a day in U.S.

- June 2017, Ohio AG filed lawsuits against 5 Pharm companies "flooded Ohio with prescription painkillers creating patients who are physically and psychologically dependent" Other cities and states have joined
- 35,000 heroin or opioid ODs 2015 (National Institute on Drug Abuse)
- Aug 7th, 2017 UVA study reports mortality rates underreported by 24% for opioids and 22% for heroin

CDC Prescribing Guidelines 2016

- Increase communication/improve understanding among providers and patients concerning risks/benefits of opioid use/chronic pain management
- Improve safety and effectiveness of pain treatment
- Reduce risks of long-term opioid therapy

Post-Op Opioid Prescribing

- Following release of the *CDC Guideline,* focus has been on opioid use for noncancer chronic pain
- Little focus devoted to nonmedical use of post op prescriptive opioids
  - Many patients first exposed to opioids after surgery
  - Need to minimize introduction of opioids into circulation by reducing avoidable exposure

Persistent Opioid Use after Surgery

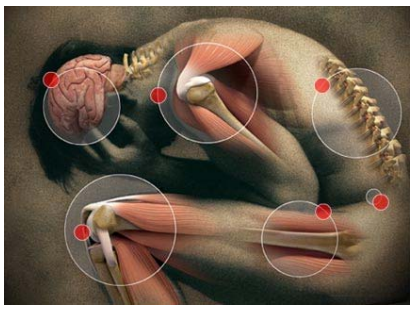
(Bickett, *JAMA Surg, 2017)*

- ~50 million ambulatory surgical procedures performed in the US in 2010
  - >2 million individuals/yr may transition to persistent opioid use
  - May be higher when including inpatient surgical procedures and considering the growth in surgical care
  - Prevalence of unused opioids after surgery →

Urologic	67%
Orthopedic	77%
Thoracic	81%
Dermatologic	89%
C-section	90%
Dental	91%
General	92%

Storage & Disposal of Opioids after Surgery

- Storage prescription opioids
  - Medicine cabinet/other box:
    - 54-70%
  - Cupboard or wardrobe:
    - 21-26%
  - Unlocked location:
    - 73-77%
- Opioid disposal
  - Planned to/actually disposed of unused opioids:
    - 4-30%
  - Considered/used method recommended by FDA:
    - 4-9%



Opioids & Pain

- A potent weapon
- A vicious adversary
- BOTH of whom must be respected

U.S. Nursing Response

- April 2016, AACN announces nursing schools commitments to combat opioid use disorder
- AACN, American Association of Nurse Anesthetists, American Association of Nurse Practitioners, American College of Nurse-Midwives, American Nurses Association, National Association of Clinical Nurse Specialists, and National Organization of Nurse Practitioner Faculties unite in joint educational series for practicing nurses, faculty and students
- Set up a 4 part webinar on the opioid crisis in Fall 2016. Available for free CEUs

Nurse Anesthesia Professional Pain Education

- Specialty pain training began 2008, now basic and advanced with didactic training and cadaveric training
- Post Master's Certificate in Advanced Pain Management Hamline University 2011-2015, moved to Fellowship 2014
- Pain Management Fellowship Texas Christian University 2016, University of South Florida 2017, Middle Tennessee 2016
- National Board for Certification and Recertification of Nurse Anesthetists certification exam began in 2015 Non-Surgical Pain Management (NSPM-C)

ERAS

- Provides a pathway to limit/avoid perioperative influencers of the opioid crisis
  - Central analgesic principle: multimodal pain therapies will reduce dependence on opioids
- Perioperative providers must carefully consider analgesia and alternatives, but must now also consider the opioid crisis impact

So the pendulum swings...

UNRELIEVED PAIN

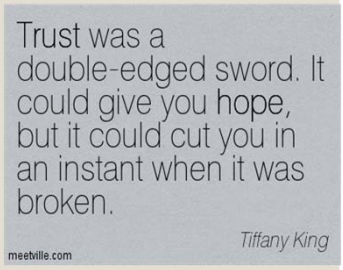
- Delays discharge or requires hospitalization
- Decreases ability to participate in Rehab
- Delays recovery and return to normal activities
- Ineffective treatment increases possibility of progression to chronic or neuropathic pain
- Associated with poor treatment outcomes
- Increased use of healthcare resources
- Increased cost of care

Best Practices in Pain Management

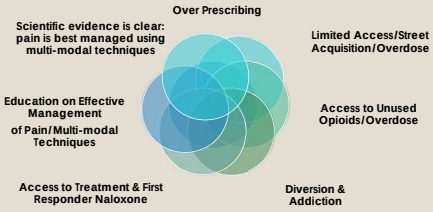
- Scientific evidence is clear: pain is best managed using multi-modal techniques
- There is a place for opioid use but it is not suitable for long term, chronic pain management
- We must **educate ALL** of our healthcare providers in best practices in pain management
- ERAS demonstrates effectiveness in decreasing opioid use

So… what is the best course of action?

- Evaluation of each individual patient
  - Pros & cons of opioids in:
    - The individual patient, having
    - The specific procedure
- Opioid free or minimizing alternatives
- Careful utilization of opioids
- Even more careful prescribing
- Trust but verify…



Response to the Opioid Crisis



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